

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently Amended) A homogenous solid or semi-solid gelatin pharmaceutical composition comprising:
 - (a) particles of at least one active agent having an effective average particle size of less than about 2000 nm prior to inclusion in the solid or semi-solid gelatin pharmaceutical composition;
 - (b) at least one surface stabilizer adsorbed on the surface of the particles;
 - (c) water in the amount from about 45% 33% to about 90% 92% based on the total weight of the composition; and
 - (d) a gel matrix of at least one gel forming substance, selected from the group consisting of a natural gelatin, a semi-synthetic gelatin, and a synthetic gelatin, the gel forming substance in an amount which exhibits gelation sufficient to retain the water,
wherein the nanoparticulate active agent particles with the adsorbed surface stabilizer are homogenously dispersed throughout the gel matrix.
2. (Original) The composition of claim 1, wherein the concentration of the at least one active agent is selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the at least one active agent and at least one surface stabilizer, not including other excipients.
3. (Original) The composition of claim 1, wherein the concentration of the at least one surface stabilizer is selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5%%, by weight, based on the total combined dry weight of the at least one active agent and at least one surface stabilizer, not including other excipients.

4. (Previously Presented) The composition of claim 1, wherein the concentration of the at least one gel forming substance is selected from the group consisting of from about 0.5% to about 60%, from about 3% to about 40%, and from about 5% to about 20%, by weight, based on the total weight of the composition.
5. (Cancelled)
6. (Cancelled)
7. (Previously Presented) The composition of claim 1, wherein the gel forming substance is a natural gelatin selected from the group consisting of algal, botanical, microbial, and animal.
8. (Original) The composition of claim 7, wherein the gel forming substance is a natural gelatin selected from the group consisting of agar, furcelleran, alginate, carrageenan, plant extracts, gum arabic, tragacanth, karaya, ghatti seed gums, guar gum, locust bean gum, xanthan, pullulan, scleroglucan, curdlan, dextran, gellan, chitin, chitosan, chondroitin sulfate, dermatan sulfate, heparan, keratan sulfate, and hyaluronic acid.
9. (Withdrawn-Currently Amended) The composition of claim 1, wherein the gel forming substance is a synthetic gelatin which is a water-soluble polymer containing complexing groups which is crosslinked to form a gel.
10. (Withdrawn) The composition of claim 9, wherein the water-soluble polymer is selected from the group consisting of acrylic acid, methacrylic acid, acrylamide, N-alkylacrylamide, methacrylamide, vinylpyrrolidone, methyl methacrylate, hydroxyethyl methacrylate, and vinyl pyridine.
11. (Withdrawn) The composition of claim 9, wherein the complexing group is selected from the group consisting of N,N'-methylenebisacrylamide and proteins.
12. (Original) The composition of claim 1, wherein the effective average particle size of the active agent particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less

than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

13. (Cancelled)
14. (Previously Presented) The composition of claim 1, wherein the composition has been molded into a shape selected from the group consisting of a geometric shape, an animal shape, a numeric shape, a character shape, and an alphabet shape.
15. (Previously Presented) The composition of claim 1, wherein the composition is formulated for administration via a route selected from the group consisting of oral, rectal, vaginal, local, buccal, and topical.
16. (Original) The composition of claim 1 formulated into a dosage form selected from the group consisting of immediate release formulation, controlled release formulation, fast melt formulation, delayed release formulation, extended release formulation, pulsatile release formulation, and mixed immediate release and controlled release formulation.
17. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.
18. (Previously Presented) The composition of claim 1, wherein the at least one active agent is in the form selected from the group consisting of crystalline particles, amorphous particles, or semi-crystalline particles.
19. (Original) The composition of claim 1, wherein the at least one active agent is poorly soluble in at least one liquid media, wherein “poorly soluble” is defined as a solubility

in the liquid media selected from the group consisting of less than about 30 mg/mL, less than about 20 mg/mL, less than about 10 mg/mL, and less than about 1 mg/mL.

20. (Original) The composition of claim 19, wherein the liquid media is selected from the group consisting of water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, and glycol.
21. (Original) The composition of claim 1, wherein the at least one active agent has been rendered poorly soluble in at least one liquid media by conjugation to a salt or other suitable substance.
22. (Previously Presented) The composition of claim 1, wherein the at least one active agent is selected from the group consisting of COX-2 inhibitors, anticancer agents, NSAIDS, proteins, peptides, nutraceuticals, anti-obesity agents, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid, calcitonin, biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anorectics, sympathomimetics, thyroid agents, vasodilators, xanthines, acne medication, alpha-hydroxy formulations, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, and respiratory illness therapies associated with acquired immune deficiency syndrome.

23. (Withdrawn) The composition of claim 22, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, healing foods that have medical or pharmaceutical effects on the body, folic acid, fatty acids, fruit and vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics.
24. (Original) The composition of claim 1, wherein the active agent is selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.
25. (Original) The composition of claim 1, wherein the active agent is selected from the group consisting of an analgesic, ketoprofen, and naproxen.
26. (Original) The composition of claim 1, comprising at least two surface stabilizers.
27. (Original) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an ionic surface stabilizer, an anionic surface stabilizer, a

cationic surface stabilizer, a nonionic surface stabilizer, and a zwitterionic surface stabilizer.

28. (Original) The composition of claim 1, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isonylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.
29. (Withdrawn) The composition of claim 27, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid,

cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈) dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈) dimethyl-benzyl ammonium chloride, N- tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl dodecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-dodecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethyl ammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide,

tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salts polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

30. (Original) The composition of any of claims 27 or 29, wherein the composition is bioadhesive.
31. (Previously Presented) The composition of claim 1, wherein the time to T_{max} of the active agent, when assayed in the plasma of a mammalian subject following administration, is less than the time to T_{max} for a non-nanoparticulate form of the same active agent, administered at the same dosage.
32. (Previously Presented) The composition of claim 31, wherein the time to T_{max} is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, and not greater than about 10% of the time to T_{max} , exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.
33. (Original) The composition of claim 1, wherein the C_{max} of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max} for a non-nanoparticulate form of the same active agent, administered at the same dosage.
34. (Original) The composition of claim 33, wherein the C_{max} is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the C_{max} exhibited by a non-

nanoparticulate formulation of the same active agent, administered at the same dosage.

35. (Original) The composition of claim 1, wherein the AUC of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.
36. (Original) The composition of claim 35, wherein the AUC is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the AUC exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.
37. (Original) The composition of claim 1 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.
38. (Original) The composition of claim 37, wherein the difference in absorption of the active agent composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.
39. (Original) The composition of claim 1, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.
40. (Original) The composition of claim 39, wherein “bioequivalency” is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

41. (Original) The composition of claim 39, wherein “bioequivalency” is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max}, when administered to a human.
42. (Original) The composition of claim 1, wherein upon administration the composition redisperses such that the active agent particles have an effective average particle size selected from the group consisting of less than about 2000 nm, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.
43. (Original) The composition of claim 1, wherein the composition redisperses in a biorelevant media such that the active agent particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

44. (Withdrawn-Currently Amended) A method of preparing a homogenous solid or semi-solid gelatin composition comprising:
- (a) combining:
- (i) a nanoparticulate active agent composition comprising particles of at least one active agent and at least one surface stabilizer adsorbed on the surface of the particle, wherein the active agent particles have an effective average particle size of less than about 2000 nm, and
- (ii) at least one gel forming substance selected from the group consisting of a natural gelatin, a semi-synthetic gelatin, and a synthetic gelatin in an amount which exhibits gelation sufficient to retain the water which exhibits gelation sufficient to retain excess water in a solid or semi-solid form, to form a solid or semi-solid dose matrix surrounding the nanoparticulate active agent composition; and
- (b) forming a solid dose formulation wherein the nanoparticulate active agent particles with the adsorbed surface stabilizer are homogenously dispersed throughout the gel matrix,
- wherein such formation does not comprise solubilizing the at least one active agent, and wherein the solid or semi-solid dosage formulation comprises from about 45% 20% to about 90% 97% water, based on the total weight of the composition.
45. (Withdrawn-Currently Amended) A method of treating a subject comprising administering to the subject an effective amount of a homogenous solid or semi-solid gelatin formulation, wherein the formulation comprises:
- (a) particles of at least one active agent having an effective average particle size of less than about 2000 nm prior to inclusion in the dosage form;
- (b) at least one surface stabilizer adsorbed on the surface of the particle; and
- (c) at least one gel forming substance selected from the group consisting of a natural gelatin, a semi-synthetic gelatin, and a synthetic gelatin in an amount which exhibits gelation sufficient to retain the water which exhibits gelation

~~sufficient to retain excess water~~, in a solid or semi-solid state, wherein the gel forming substance forms a matrix surrounding the nanoparticulate active agent particles and surface stabilizer,

wherein the nanoparticulate active agent particles with the adsorbed surface stabilizer are homogenously dispersed throughout the gel matrix, and

wherein the formulation comprises from about 45% 20% to about 90% 97% water, based on the total weight of the composition.

46. (Withdrawn) The method of claim 45, wherein the subject is fasted prior to administration.
47. (Currently Amended) A solid or semi-solid gelatin pharmaceutical composition comprising:
 - (a) particles of at least one active agent having an effective average particle size of less than about 2000 nm prior to inclusion in the solid or semi-solid gelatin pharmaceutical composition;
 - (b) at least one surface stabilizer adsorbed on the surface of the particles; and
 - (c) a gel matrix of at least one gel forming substance, the gel forming substance in an amount which exhibits gelation sufficient to retain water in an amount of from 45% 33% to about 90% 92% based on the total weight of the composition,

wherein the nanoparticulate active agent particles with the adsorbed surface stabilizer are dispersed in the gel matrix,

wherein the composition is made by a process comprising the steps:

 - (i) heating the at least one gel forming substance to form a molten composition;
 - (ii) adding the particles of at least one active agent and at least one surface stabilizer to the molten gel forming substance composition;
 - (iii) mixing the composition resulting from combining (i) and (ii); and

(iv) refrigerating the composition of step (iii) until a solid or semi-solid pharmaceutical composition is obtained.